IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Yoe et al.

Examiner: Camtu Tran Nguyen

Serial No.: 09/872,135

Art Unit: 3743

Filed: May 31, 2001

Title: Radiation Or Drug Source With Activity Gradient To Minimize Edge Effects

---

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 CFR § 1.131

We, Brandon J. Yoe and Arthur Au, declare as follows:

1. Prior to April 12, 2001, we conceived of or invented the subject matter of the claims in the application identified above.

2. We have attached a redacted copy of an invention disclosure form showing the subject matter of the invention. As can be seen, this selection of pages shows conception of the invention prior to April 12, 2001.

3. The subject matter of the invention was reduced to practice in a diligent manner, as at least shown by the constructive reduction to practice of the invention merely forty-nine (49) days after the filing date of the Hossainy et al. reference (USPN 6,764,505). In particular, the filing date of the Hossainy et al. reference was April 12, 2001, while the filing date of the current application was May 31, 2001.

4. We further declare that all statements made herein of our own knowledge are true and that all statements made upon information and belief are believed to be true; and further that

these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Executed in California on this _____ day of July __, 2005.

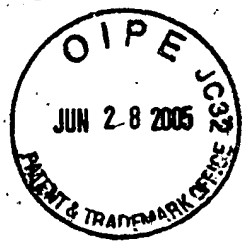
By:_____
Brandon J. Yoe
Employee of
Advanced Cardiovascular Systems, Inc.

Executed in California on this _____ day of July __, 2005.

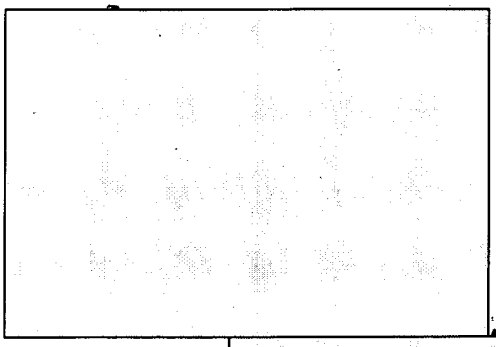
By:_____
Arthur Au
Former Employee of
Advanced Cardiovascular Systems, Inc.

Squire, Sanders & Dempsey L.L.P.
One Maritime Plaza, Suite 300
San Francisco, CA 94111-3492
Telephone (415) 954-0345
Facsimile (415) 393-9887

header not part of original

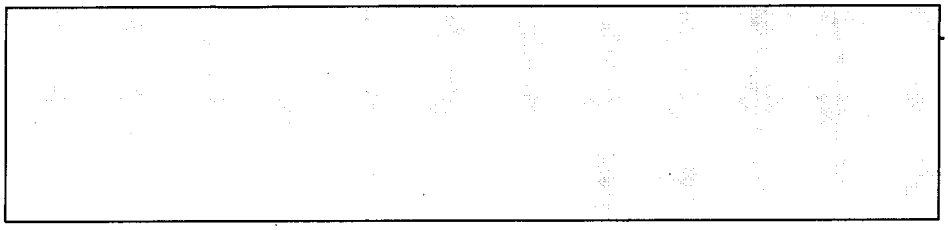


Appendix



INVENTION DISCLOSURE FORM

ADVANCED CARDIOVASCULAR SYSTEMS, INC.



header not part of original

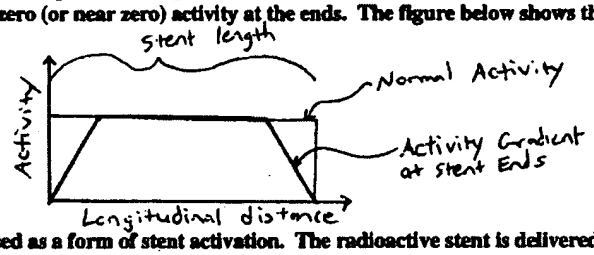
1. DESCRIPTIVE TITLE OF THE INVENTION:

Longitudinal Radioactive Stent Activity Gradient to Eliminate Edge Effects

2. Submitter(s): *(please provide your full name, including middle name)*

Inventors initials:
1 2 3 4 5 6 7 8 9

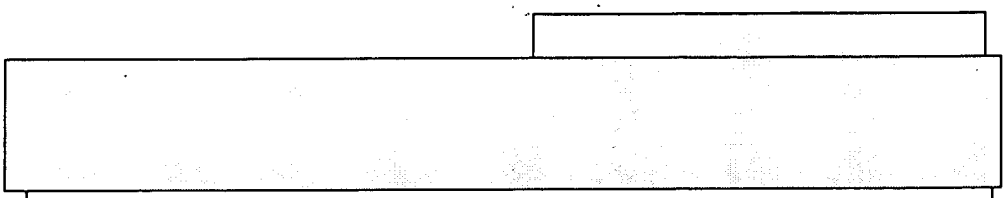
(a) Radioactive stents emit radiation that inhibits cell proliferation and therefore inhibits restenosis from occurring in vascular sites. However, there is an anomalous effect at the stent edges where a narrowing of the vessel may occur. This invention targets a reduction or elimination of the edge effect by introducing a more gradual dose gradient at the stent edges. This is accomplished by activating the stent such that the radiation profile has a gradual transition from the target radiation levels in the middle of the stent, to zero (or near zero) activity at the ends. The figure below shows the activity profile of such a stent:



(b) This invention is used as a form of stent activation. The radioactive stent is delivered to the site of revascularization using a catheter and is implanted to maintain patency.

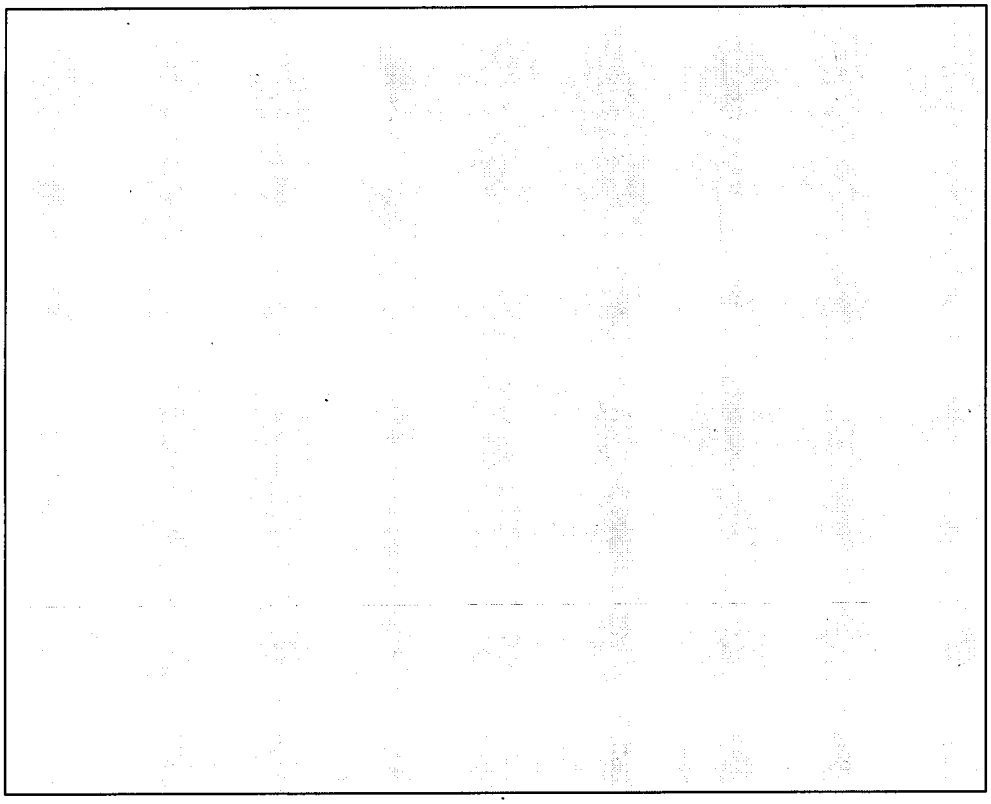
(d) This form of stent activation is intended to minimize the presence of a rapid dose drop-off at the edges of a radioactive stent. The presence of this rapid dose drop-off results in an interface between injured (radiated) and non-injured tissue that may cause the edge stenosis associated with radioactive stenting known as the "edge-effect" or the "candy-wrapper effect." Therefore, this form of stent activation is intended to reduce or eliminate the edge-effect.

(See attachments from Lab Notebook #5640, pp. 28-33, dated 13 June 2000.)



This stent activity gradient could be used to eliminate edge effects resulting from radioactive stents in all arteries (coronary and peripheral) and potentially in non-vascular ducts. It could also be applied to edge effects in other stents that have therapeutic agents and could result in edge effects (such as a drug delivering stent).

The length of the gradient may be varied to meet the clinical need depending on the vessel, the isotope, or the activity. This needs to be determined using animal and/or clinical data.



Read and understood the completed Invention Disclosure Form

Signature 6-22-00 Date

header not part of original

28 **TITLE** Longitudinal Radioactive Stent Activity Gradient to Eliminate Edge Effects **PROJECT NO.** **BOOK NO.**

Work continued from Page N/A

DATE: 13 June 2000

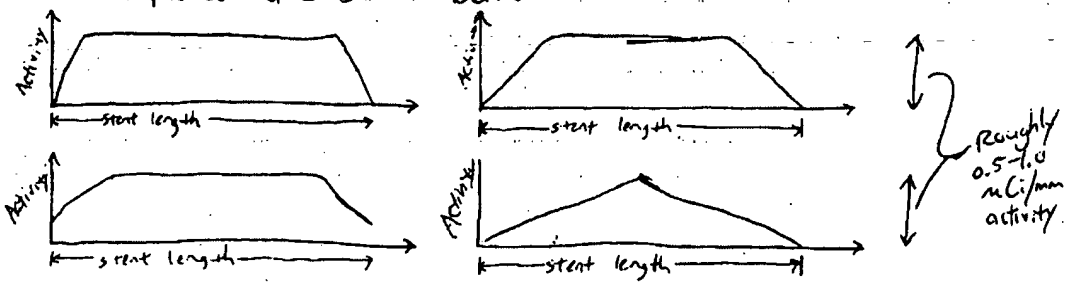
CONCEPT/IDEA DESCRIPTION:

Radiation emitting stents have been shown to inhibit tissue proliferation in porcine and human arteries. However, there is still a proliferation at the edges of the stent that results in clinical restenosis despite patency inside the stent.

At the edge of the stent, there is a rapid transition along the longitude where the radiation dose goes from anti-proliferative to nothing (near zero). Because the radiation dose can be considered a form of injury, the rapid transition results in a interface of injured tissue and healthy tissue. The edge effect may be the proliferative response of the healthy (and non-irradiated) tissue to the neighboring tissue that is injured (but still not proliferating due to the radiation dose in that region).

The rapid longitudinal dose transition and resulting injured/non-injured tissue interface can be minimized by creating a gradual or shallower dose gradient from the ~~center~~ body of the stent to the stent edge and past. 6/13/00

Such a dose gradient could be created using a stent that has an activity gradient along its length/longitude. Potential gradients to be explored are shown below:



SCIENTIFIC BINDERY PRODUCTIONS CHICAGO 60605 MADE IN USA

Work continued to Page 29

SIGNATURE [signature] DATE 6/13/00

DISCLOSED TO AND UNDERSTOOD BY Céline Machut DATE 6.14.2000 WITNESS DATE

header not part of original

TITLE **PROJECT NO.** **29**

BOOK NO.

Work continued from Page 28

The mid or peak activity would simply be the target activity for current radioactive stenting. The length of the gradient on the ends would need to be investigated using animal and clinical studies if possible. The end activity would be approaching zero so that no rapid transition would still exist. However, it is possible that below a threshold value or total drop threshold, the gradient may not be as important, and the edge activity could still be some non-zero value.

The activity gradient could be created in different ways depending on the activation method being used. For ion implantation, the ion beam can spend less and less time toward the edges. Additionally, a masking and unmasking technique could be used (this would also work for plasma ion implantation or coating methods of activation).

ATTACHMENTS:

On pages 30 - 33 of this labnotebook (#5840), there are photocopies of several entries in my personal lab notebook #02, "Radiation", discussing animal study methods to test and explore the benefit of such an activity gradient. (Pages were numbered 33-36 in the personal notebook.)

6/13/00

SCIENTIFIC BINDERY PRODUCTIONS CHICAGO 60605 MADE IN USA

Work continued to Page 30

SIGNATURE

DATE 6/13/00

DISCLOSED TO AND UNDERSTOOD BY

DATE

WITNESS

DATE

Célia Machiel 6.14.2000

header not part of original

30 TITLE

PROJECT NO.

BOOK NO.

Work continued from Page 29

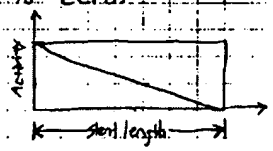
Animal Study : Assess Effects of Dose and Dose Gradient 4/24/00

Study Goals: ① Use animal model to determine level of 1 month dose that creates stenosis (or range of doses) – ie. the subtherapeutic dose or counter-therapeutic dose level.

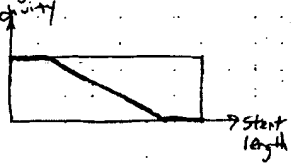
② Use animal model to determine whether or not varying the dose/dose rate gradient or drop-off rate affects the size and/or degree of stenosis at 1 month.

Possible Methods:

Both goals can be achieved using one study that varys the gradient along the stent. The dose(s) identified as having a proliferative effect should be compared to the previous dose-finding animal studies. The dose gradient can be created by varying the dose rate (ie the steat activity) linearly along the length from some value down to zero.



Because it is known that edge effects exist when using radioactive stents (under current conditions), the activation should be done to minimize this effect on the gradient region. This can be accomplished as shown below:



This activation profile will make sure that any edge anomalies that occur will be outside of the gradient region and any stenosis in the gradient will be "uncontaminated" by the edges and other factors besides the gradient itself and the [illegible] itself.

READ & UNDERSTOOD BY: Celina Machuca 6/14/00 B. Hyde 6/14/00 Dave Hy 6/13/00

Continued to Page 31

SIGNATURE

DISCLOSED TO AND UNDERSTOOD BY Celina Machuca DATE 6.14.2000 WITNESS

DATE 6/14/00

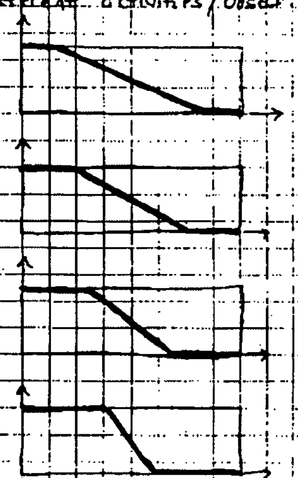
DATE

TITLE **PROJECT NO.** **BOOK NO.**

Work continued from Page 30

Cont'd (Animal Study) 4/21

several different stents with different activity gradient can be implanted to explore the effects on proliferation across the same range of doses. With the edge buffers, the stents can be of consistent length. Holding the peak activity constant and changing the distance over which it goes to zero will eliminate uncertainty involved in using different activities/doses.



Assuming that the effectiveness of radiation has a neg. effect on proliferation below the current levels used, and that this effect reverses as the activity/dose/dose rate approach zero, then the appropriate low activity should be zero. The high side should be as low as is believe to be effective but still higher than the low dose proliferative level. This will ensure the greatest amount of resolution. This value is roughly 0.5 uCi/mm.

The gradient should be as low as possible and then at least as steep or steeper than the transition for the hot end stents. Presumably, the steep gradients will show a proliferation but at some point, as the gradient gets more gradual, the proliferative effect will disappear. Identifying where/when will influence activation strategies for clinical implementation. The Hot Ends gradient for the Hot End study should be reviewed

continued to Page 32

READ AND UNDERSTOOD BY: [signature] 6/14/00

[signature] 6/14/00

[signature] 6/13/00

SIGNATURE [signature] **DATE** 6/14/00

DISCLOSED TO AND UNDERSTOOD BY [signature] **DATE** 6-14-2000 **WITNESS** **DATE**

header not part of original

32 TITLE

PROJECT NO.

BOOK NO.

Work continued from Page 31

35

Contd (Animal Study) 4/24 cont'd

If the gradient is not shown to affect proliferation and dose is shown to have an effect, we should expect to see a decreasing length over which the proliferation occurs because the length of critical dose(s)/dose rate(s) will shorten with increased gradient. This effect will likely be limited and complicated by the nature of blood flow and other biologic factors that may not allow regions of proliferation to be shorter than some actual limit.

B. Apfel 6/14/00

6/14/00

B. Apfel

Work continued to Page 33

SIGNATURE B. Apfel DATE 6/14/00

DISCLOSED TO AND UNDERSTOOD BY Celine Machuret DATE 6.14.2000 WITNESS DATE

header not part of original

TITLE **PROJECT NO.** **BOOK NO.** **33**

Work continued from Page 32

36

GRADIENT STENT DESIGN OF ANIMAL STUDY — May 4, 2000

Possible Theories to Test for Cause of Edge Effect

(1) There exists a dose at which proliferation is encouraged.

(2) There exists a dose rate at which proliferation is encouraged. (By this theory, the whole stent would stenose; unless, this theory only applys to injured tissue and overtime healing can counter this)

(3) There is a dose gradient effect such that a quick drop off or change in dose (longitudinally) causes a healthy tissue: injured tissue interface where the healthy tissue overreacts.

(4) The current edge effect is caused by (2), but (1) is also true. However, (1) is not the cause in the current stenting practice because the gradient is so steep that the region of "bad" dose is too small to matter. But, at longer drop offs this region increases and could then cause a stenosis. For this theory, a very short and a very long gradient may both produce proliferation, but an intermediate gradient would not (or could be optimized at the least).

READ & UNDERSTOOD BY: Elaine Marshall 6/14/00 — R. Taylor 6/14/00

CONTINUATION ON GRADIENT ANIMAL STUDY — May 5, 2000

- The Human reaction to radiation appears to be greater than the porcine model w.r.t. unwanted proliferation at the regions of radiation transistion. With this in mind, a change in activity (and dose) change gradient may have an effect in the pig over a short range of steeper gradients than a longer range of shallower gradients in the human. This would explain why a 2mm gradient may be enough to eliminate edge effects in a pig B/C this is so small and cannot easily be produced/measured (stent activity), it would be a challenge to prove that the gradient has an effect using the porcine model even though it may have an

B. Taylor 6/13/00

to Page N/A

SIGNATURE B. Taylor DATE 6/14/00

DISCLOSED TO AND UNDERSTOOD BY Elaine Marshall DATE 6-14-2000 WITNESS DATE